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Scientific paper

Synthesis and Antimicrobial Evaluation of Some New Pyrazolo[1,5-*a*]pyrimidine and Pyrazolo[1,5-*c*]triazine Derivatives Containing Sulfathiazole Moiety

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Abstract

A number of important fused heterocyclic systems have been prepared by the reaction of 4-((3,5-diamino-1*H*-pyrazol-4-yl)-diazenyl)-*N*-(thiazol-2-yl)-benzenesulfonamide with some bifunctional nucleophiles such as ethyl acetoacetate, acetylacetone or arylidenemalononononitrile derivatives to obtain pyrazolo[1,5-*a*]pyrimidine derivatives. The structures of the newly synthesized compounds were determined based on their IR, ^{1}H and ^{13}C NMR and mass spectroscopic data. Most of the compounds produced showed good antibacterial and antifungal activity.

Keywords: Sulfathiazole; benzenesulfonamide; pyrazole; antimicrobial evaluation.

1. Introduction

It is known that sulfathiazole derivatives have a decisive new and differentiating application in various areas of chemistry.[1–3] The pyrazole skeleton is a common core in many pharmaceutically active compounds and is important for a wide range of pharmacological activities including anti-inflammatory,[4,5] antiviral,[6] antimicrobial,[7] antifungal,[8,9] hypoglycemic,[10,11] antihyperlipidemic,[12] cyclooxygenase-2 inhibitors,[13] CDK2/cyclinA inhibitors,[14,15] and anti-angiogenic activity.[16] Furthermore, carbonyl cyanide-phenylhydrazone is an efficient decoupler of oxidative phosphorylation sites in a mitochondrial organism.[17] In this study, arylhydrazonomalononitrile was prepared and used as a reactive intermediate in the synthesis of various heterocyclic compounds with expected critical biological activity. Therefore, we report here on the synthesis of some new sulfathiazole derivatives to investigate their antimicrobial activity.

2. Experimental

All melting points were determined with the electrical melting point device from Gallenkamp and are uncorrected. Precoated Merck Silica gel plates 60F-254 were used for thin layer chromatography (TLC) and the spots were detected under UV light (254 nm). The infrared spectra (IR) were recorded with a Mattson 5000 FTIR spectrophotometer (KBr plate). The NMR spectra were recorded on Varian Gemini spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR). Deuterated DMSO-d_6 was used as solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts were measured in δ ppm relative to the TMS. Mass spectra were determined with a GC-MS QP-100 EX Shimadzu instrument, and elemental analysis was performed with a Perkin-Elmer 2400 elemental analyzer.

Synthesis of N-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyl dicyanide (2)

To a solution of malononitrile (0.66 g, 10 mmol) in ethanol (30 ml) 0,5 g anhydrous sodium acetate was added. The solution was then treated with a solution of diazonium salt of p-aminosulfathiazole (prepared from (2.55 g, 10 mmol p-aminosulfathiazole and the corresponding quantities of hydrochloric acid and sodium nitrite). The reaction mixture was stirred for 1 hour and the resulting

solid was filtered off, washed with water and recrystallized from ethanol to compound **2**. Golden yellow crystals; yield: 90%; mp 215–220 °C ; IR (KBr): ν 3234, 3188 (2NH), 2225 and 2216 (2CN), 1654 (C=N) 1565 (N=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.81(d, 1H, H-5, thiazole ring, *J*=4.2), 7.21(d, 1H, H-4, thiazole ring, *J*=4.2), 7.75 (d, 2H, Ar-H, *J*=8.5), 8.00 (d, 2H, Ar-H, *J*=8.5), 11.61 (s, 1H, NH), 12.30 (s, 1H , $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 85.6, 112.3, 114.5, 116.8, 129.7, 132.0, 139.6, 147.9, 171.5 ppm; MS: *m/z* (%) 332 (M^+, 31.8), 257 (49), 71 (44), 55 (72), 43 (100). Anal. Calcd. for $C_{12}H_8N_6O_2S_2$ (332.36): C, 43.37; H, 2.52; N, 25.29 %. Found: C, 43.51; H, 2.63; N, 25.39 %.

Synthesis of 4-((3,5-diamino-1H-pyrazol-4-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (3)

A mixture of **2** (3.32 g, 10 mmol) and hydrazine hydrate (0.5 ml, 10 mmol) was added to ethanol (10 ml) under reflux for 3 hours and then cooled to room temperature. The precipitate formed was collected by filtration, dried and recrystallized from a mixture of DMF/EtOH (1:1) to obtain compound **3**. Yellow needles crystals; yield: 78%; mp 235–240 °C; IR (KBr): ν 3430, 3373, 3337, 3289, 3219 ($2NH_2$ and 2NH) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.27 (s, 4H, $2NH_2$), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.64 (s, 1H, $NHSO_2$), 12.66 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.5, 112.4, 127.9, 129.7, 132.0, 139.6, 137.9, 151.5, 171.9 ppm; MS: *m/z* (%) 364 (M^+, 0.9), 275 (49) 147 (10), 97(34), 57 (81); Anal. Calcd for $C_{12}H_{12}N_8O_2S_2$ (364.40): C, 66.49; H, 4.82; N, 24.67%. Found: C, 66.43; H, 4.90; N, 24.70%.

General procedure for the reaction of 3,5-aminopyrazole 3 with ethylacetoacetate and 1,3 dicarbonyl compound (acetyl aceton) toward formation of compounds 5 and 6

To a solution of compound **3** (0.3 g, 1 mmol) in glacial acetic acid (25 ml) the corresponding 1,3-dicarbonyl compound such as ethyl acetoacetate and acetylacetone (1 mmol) was added. The reaction mixture was refluxed for 3 hours under reflux in a sand bath and then poured onto crushed ice. Shaped precipitate was collected by filtration, washed with ethanol, dried and recrystallised from a mixture of DMF/EtOH (1:1) to compounds **5** and **6** respectively.

4-((2-Amino-7-methyl-5-oxo-4,5-dihydropyrazolo[1,5-a]pyrimidin-3-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (5)

Orange crystals; yield: 75%; mp 230–235 °C; IR (KBr): ν 3444–3380 (NH_2 and NH), 1661 (CO) cm^{-1}; ^1H NMR(400 MHz, DMSO-d_6): δ 2.01(s, 3H, CH_3), 6.27(s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.26 (s, 1H, pyrimidine ring), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 11.46 (s, 1H, NHCO), 12.64 (s, 1H, $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.2, 76.9, 104.3, 112.2, 127.4, 129.2, 131.9, 137.1, 139.8, 146.8, 147.9, 161.3, 171.8 ppm; MS: *m/z* (%) 430 (M^+, 1.0), 139 (28), 110 (19), 82 (29), 63 (40), 43 (100); Anal.Calcd for $C_{16}H_{14}N_8O_3S_2$ (430.46): C, 44.64; H, 3.28; N, 26.03%; Found: C, 44.73; H, 3.32; N, 26.08%.

4-((2-Amino-5,7-dimethylpyrazolo[1,5-a]pyrimidin-3-yl)diazenyl)-N-(thiazol-2-yl) benzenesulfonamide (6)

Brown powder; yield: 80%; mp 225–230 °C ; IR (KBr): ν 3437–3394 (NH_2 and NH), 1560 (N=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.08 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 5.74 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.08 (s, 1H, pyrimidine ring), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.67 (s, 1H, $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.7, 24.5, 87.8, 108.9, 112.3, 127.5, 129.4, 131.6, 137.7 139.8, 145.8, 152.8, 164.9, 171.9 ppm; MS: *m/z* (%) 428 (M^+, 7.0), 395 (28), 369 (17), 313 (22), 201 (50), 183 (38), 130 (68), 92 (100). Anal. Calcd for $C_{17}H_{16}N_8O_2S_2$ (428.49): C, 47.65; H, 3.76; N, 26.15%; Found: C, 47.74, H, 3.79, N, 26.20%.

General procedure for the reaction of 3,5-amino pyrazole (3) with 2-(4-chloro and 4-nitro benzylidene)malononitrile:

To a solution of compound **3** (0.3 g, 1 mmol) in ethanol (25 ml) the corresponding arylidene was added, namely 2-(4-chlorobenzylidene)malononitrile (0.189 mg, 1 mmol) and 2-(4-nitrobenzylidene)malononitrile (0.2 g, 1 mmol) containing a catalytic amount of pipridine. The reaction mixture was refluxed for 3 hours to obtain compounds **7** and **8**, respectively.

4-((2,5-Diamino-7-(4-chlorophenyl)-6-cyanopyrazolo[1,5-a]pyrimidin-3-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (7)

Brown powder; yield: 81%; mp 240–245 °C ; IR (KBr): ν 3435–3300, 2191 (for $2NH_2$, NH and CN functional groups) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.28 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.54 (s, 2H, NH_2), 7.56 (d, 2H, Ar-H), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 7.98 (d, 2H, Ar-H), 12.64 (s, 1H, $NHSO_2$) ppm; MS: *m/z* (%) 551 (M^+, 10), 553 (M^++2, 1), 386 (28), 280 (35), 242 (28), 185 (75), 139 (57), 105 (71), 69 (61), 42 (52); Anal. Calcd for $C_{22}H_{15}ClN_{10}O_2S_2$ (551.00): C, 47.96; H, 2.74; N, 25.42%; Found: C, 47.86, H, 2.68, N, 25.34%.

4-((2,5-Diamino-6-cyano-7-(4-nitrophenyl)pyrazolo[1,5-a]pyrimidin-3-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (8)

Dark brown powder; yield: 82%; mp 265–270 °C ; IR (KBr) ν 3426–3399, 2212, 1530 ($2NH_2$, NH, CN and NO_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.28 (s, 2H, NH_2),

6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.53 (s, 2H, NH_2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 7.98 (d, 2H, Ar-H), 8.29 (d, 2H, Ar-H), 12.64 (s, 1H, $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 87.4, 88.3, 112.8, 116.2, 124.5, 126.3, 127.4, 129.2, 131.5, 137.3, 139.2, 140.9, 147.1, 147.8, 152.7, 165.6, 169.9, 171.8 ppm; MS: *m/z* (%) 561 (M^++1, 10), 331 (83), 267 (100), 185 (54), 157 (25), 116 (31), 48 (28); Anal. Calcd for $C_{22}H_{15}N_{11}O_4S_2$ (561.56): C, 47.06; H, 2.69; N, 27.44%; Found: C, 47.13, H, 2.71, N, 27.40%.

Synthesis of 4-((3-amino-5-(3-phenylthioureido)-1H-pyrazol-4-yl)diazenyl)-N-(thiazol-2-yl) benzenesulfonamide (9)

Compound **3** (0.3 g, 1 mmol) was added to a solution of phenyl isothiocyanate (1 mmol) in pyridine (10 ml) and the reaction mixture was refluxed for 3 hours. The mixture was then poured into crushed ice, a few drops of HCl were added and the resulting solid was filtered and recrystallized from ethanol to obtain compound **9**. Brown powder; yield: 76%; mp 245–250 °C ; IR (KBr) ν 3444, 3424 (NH_2 and 4NH), 1644–1561 (N=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.27 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.31–7.79 (m, 5H,Ar-H), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 10.7 (s, 1H, NHC=S), 11.20 (s, 1H, NHC=S), 12.42 (s, 1H, NH), 12.64 (s, 1H,$NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.5, 112.2, 126.7, 127.4, 128.5, 129.1, 129.8, 131.9, 137.1, 138.6, 139.8, 151.4, 171.8, 179.9 ppm; MS: *m/z* (%) 500 (M^+, 30), 394 (7), 298 (5), 284 (19), 259 (23), 214 (10), 193 (11), 109 (63), 85 (100), 68 (68), 42 (95); Anal. Calcd for $C_{19}H_{17}N_9O_2S_3$ (499.59): C, 45.68; H, 3.43; N, 25.23%; Found: C, 45.77, H, 3.49, N, 25.25%.

General procedure for synthesis of compounds 11–14

Diazonium salt of **10** (10 mmol) was added dropwise in an ice-cold solution of malononitrile, 2-cyanoacetohydrazide, *N*-phenylacetamide and 3,5-dimethylphenol (10 mmol) in pyridine and stirred for 1 hour. The reaction mixture was then cooled and the resulting solid was collected by filtration and recrystallized from ethanol.

.4-((4,7-Diamino-3-cyanopyrazolo[5,1-c][1,2,4]triazin-8-yl)diazenyl)-N-(thiazol-2-yl) benzenesulfonamide (11)

Orange crystals; yield: 83%; mp 250–255 °C ; IR (KBr) ν 3447–3300 ($2NH_2$ and NH), 2227 (CN), 1644–1600 (N=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.27 (s, 4H, $2NH_2$), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.64 (s, 1H, $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 87.8, 112.2, 113.4, 127.4, 129.2, 131.2, 137.2, 139.8, 147.2, 149.4, 150.2, 152.8, 171.8 ppm; MS: *m/z* (%) 441 (M^+, 1), 396 (29), 357 (19), 147(17), 125 (23), 97(34), 57 (100), 69 (67), 43 (76); Anal. Calcd for $C_{15}H_{11}N_{11}O_2S_2$ (441.45): C, 40.81; H, 2.51; N, 34.90%; Found: C, 40.89, H, 2.57, N, 34.95%.

4-(3-Amino-5-((5-amino-3-oxo-3H-pyrazol-4-yl)diazenyl)-1H-pyrazol-4-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (12)

Orange powder; yield: 85%; mp 250–255 °C ; IR (KBr): ν 3417–3311 ($2NH_2$ and 2NH), 1678 (CO), 1565 (N=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.28 (s, 2H, NH_2), 6.56 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.64 (s, 1H, $NHSO_2$), 13.26 (s, 1H NH pyrazole ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 87.8, 112.2, 118.4, 127.4, 129.2, 131.2, 137.2, 139.8, 145.6, 152.7, 160.3, 167.3, 171.8 ppm; MS: *m/z* (%) 472 (M^+, 0.8), 397 (4), 285 (9), 97 (29), 63 (100), 57 (77), 43 (90); Anal. Calcd for $C_{15}H_{12}N_{12}O_3S_2$ (472.46): C, 38.13; H, 2.56; N, 35.58%; Found: C, 38.20, H, 2.64, N, 35.63%.

2-((3-Amino-4-((4-(N-(thiazol-2-yl)sulfamoyl)phenyl) diazenyl)-1H-pyrazol-5-yl)diazenyl)-2-cyano-N-phenylacetamide (13)

Red powder; yield: 83%; mp 255–260 °C ; IR (KBr): ν 3444–3300 (NH_2 and 3NH), 2220 (CN), 1678 (CO), 1565 (N=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.97 (s, 1H, CHCN), 6.27 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.17–7.53 (m, 5H, Ar-H), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 10.02 (s,1H, NHCO), 12.64 (s,1H, $NHSO_2$), 13.27 (s, 1H NH pyrazole ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 54.5, 87.4, 112.3, 114.9, 121.7, 127.4, 128.9, 129.4, 130.6, 131.9, 137.5, 138.6, 139.8, 145.7, 152.8, 168.4, 171.9 ppm; MS: *m/z* (%) 535 (M^+, 0.8), 241 (6), 215 (7), 160 (40), 94 (24), 45 (100); Anal. Calcd for $C_{21}H_{17}N_{11}O_3S_2$ (535.56): C, 47.10; H, 3.20; N, 28.77%; Found: C, 47.19, H, 3.22, N, 28.83%.

4-(3-Amino-5-((4-hydroxy-2,6-dimethylphenyl)diazenyl)-1H-pyrazol-4-yl)diazenyl)-N-(thiazol-2-yl)benzenesulfonamide (14)

Red powder; yield: 78%; mp 245–250 °C ; IR (KBr): ν 3445, 3330 (NH_2 and 2NH), 3300 (OH), 1550–1600 (N=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (s, 6H, $2CH_3$), 6.27 (s, 2H, NH_2), 6.60 (d, 2H, phenol ring), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 9.19 (s, H, OH), 12.64 (s, 1H, $NHSO_2$), 13.27(s, 1H, NH pyrazole ring) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.6, 87.8, 111.8, 112.2, 119.8, 127.4, 129.2, 131.9, 137.1, 138.4, 139.8, 145.7, 152.8, 156.4, 171.8 ppm; MS: *m/z* (%) 497 (M^+, 0.8), 394 (7), 284 (19), 259 (23), 151 (14), 109 (63), 91 (33), 85 (100), 42 (95); Anal. Calcd for $C_{20}H_{19}N_9O_3S_2$ (497.55): C, 48.28; H, 3.85; N, 25.34%; Found: C, 48.32, H, 3.80, N, 25.33%.

N-Methyl-N-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyl dicyanide (15)

K_2CO_3 (0,137 g, 1 mmol) was added to a solution of compound **2** (0,3 g, 1 mmol) in ethanol (25 ml) and stirred

for 1 hour. CH_3I (0.14 ml, 1 mmol) was then added and the solution was stirred for 12 hours. The reaction mixture was poured into crushed ice and a few drops of HCl were added. The resulting solid was filtered off and recrystallized from ethanol to compound **15**. Yellow powder; yield: 76%; mp 240–245 °C ; IR (KBr): ν 3300 (NH), 2232 (2CN), 1565–1600 (N=N), 1601 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.35 (s, 3H, CH_3), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.45 (s, 1H, $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 34.4, 84.6, 112.5, 127.6, 128.8, 130.1, 137.2, 147.2, 171.8 ppm; MS: *m/z* (%) 346 (M^+, 3.3), 332 (14), 283 (11), 267 (8), 200 (10), 191 (18), 156 (42), 93 (100), 80 (34); Anal. Calcd for $C_{13}H_{10}N_6O_2S_2$ (346.38): C, 45.08; H, 2.91; N, 24.26%; Found: C, 45.09, H, 2.95, N, 24.31%.

2-Amino-2-hydrazineylidene-N-methyl-N-(4-(N-(thiazol-2-yl)sulfamoyl)phenyl) acetohydrazonoyl cyanide (16)

Hydrazine hydrate (0,05 ml, 1 mmol) was added to a solution of compound **15** (0.3 g, 1 mmol) in ethanol (25 ml) and the reaction mixture was refluxed for 4 hours. After cooling, the reaction mixture was poured into ice water, the precipitate was collected, filtered, dried and recrystallized from EtOH/DMF to obtain compound **16**. Orange powder; yield: 77%; mp 255–260 °C ; IR (KBr): ν 3443, 3410 ($2NH_2$), 3333 (NH), 2215 (CN) cm^{-1}; ^1H NMR (400 mHz, DMSO-d_6): δ 3.34 (s, 3H, CH_3), 5.80 (s, 2H, NH_2), 6.54 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.46 (s, 1H, $NHSO_2$) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 36.8, 108.6, 112.2, 114.8, 115.2, 129.3, 130.2, 137.3, 147.4, 152.9, 171.8; MS: *m/z* (%) 378.14 (M^+, 8), 336 (31), 314 (32), 275 (31), 257 (80), 152 (59), 110 (53), 83 (100); Anal. Calcd. for $C_{13}H_{14}N_8O_2S_2$ (378.43): C, 41.26; H, 3.73; N, 29.61%; Found: C, 41.28; H, 3.77; N, 29.64%.

General procedure for the synthesis of 17 and 18

Thiourea (0.076 g, 1 mmol) and hydroxylamine hydrochloride (0.07 g, 1 mmol) containing a catalytic amount of pypridine (5 drops) were added to a solution of compound **2** (0.3 g, 1 mmol) in ethanol (25 ml) and returned under reflux for 4 hours. The reaction mixture was poured into ice water and the prepicitate collected, filtered, dried and recrystallized from EtOH with a few drops of DMF, to obtain **17** and **18** respectively.

4-(2-(4,6-Diamino-2-thioxopyrimidin-5(2H)-ylidene) hydrazineyl)-N-(thiazol-2-yl) benzenesulfonamide (17)

Brown powder; yield: 68%; mp 255–260 °C ; IR (KBr): ν 3434–3400, 1325 ($2NH_2$, 2NH and C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.58 (s, 2H, NH_2), 6.61 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 12.45 (s, 1H, $NHSO_2$), 12.86 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.2, 116.8, 129.1, 130.6, 137.2, 138.3, 147.4, 162.8, 171.8, 230.0 ppm; MS: *m/z* (%) 408 (M^+, 1), 397 (11), 353 (17), 285 (19), 258 (27), 257 (62), 168 (20), 55 (92), 43 (100); Anal. Calcd. for $C_{13}H_{12}N_8O_2S_3$ (408.47): C, 38.23; H, 2.96; N, 27.43%; Found: C, 38.28; H, 2.93; N, 27.42%.

4-(2-(3-Amino-5-iminoisoxazol-4(5H)-ylidene)hydrazineyl)-N-(thiazol-2-yl) benzenesulfonamide (18)

Deep orange powder; yield: 73%; mp 245–250 °C ; IR (KBr): ν 3444–3300, 1633 (NH_2, 3NH and N=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 6.62 (s, 2H, NH_2), 6.81 (d, 1H, H-5, thiazole ring, *J*=4.2), 7.21 (d, 1H, H-4, thiazole ring, *J*=4.2), 7.73 (d, 2H, Ar-H, *J*=8.5), 7.79 (d, 2H, Ar-H, *J*=8.5), 9.68 (s, 1H, NH isoxazole), 12.44 (s, 1H, $NHSO_2$), 12.87 (s, 1H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 112.3, 116.8, 129.8, 130.2, 136.9 137.2, 147.4, 151.8, 158.9, 171.9 ppm; MS: *m/z* (%) 365, (M^+, 8), 244 (9), 239 (16), 229 (15), 207 (21), 119 (40), 97 (91), 66 (100); Anal. Calcd. for $C_{12}H_{11}N_7O_3S_2$ (365.39): C, 39.45; H, 3.03; N, 26.83%; Found: C, 39.47; H, 3.10; N, 26.86%.

Antimicrobial studies

Whatman filter paper disks were prepared with standard size (5.0 mm diameter) and stored in 1.0 Oz screw-capped wide holders for sterilization. These bottles were stored in a hot air oven at 150 °C. The disks of sterilized standard filter paper impregnated with a solution of the test compound in DMSO (1 mg/mL) were then placed on a supplementary agar plate, which was seeded with the appropriate test organism in triplicates. Standard concentrations of 106 CFU/mL (Colony Forming U/mL) and 104 CFU/mL were used individually for the antibacterial and antifungal test. Pyrex glass petri dishes (9 cm diameter) were used and two disks of filter paper were inoculated in each plate. The test organisms used were *B. subtilis* and *S. aureus* as Gram-positive bacteria and *E. coli* and *P. aeruginosa* as Gram-negative bacteria. They were also tested for their in vitro antifungal potential against fungal strains of *F. oxysporum* and *C. albicans*. Chloramphenicol, cephalothin and cycloheximide were used individually as standard antibacterial and antifungal agents. DMSO alone was used as a control at the same concentrations mentioned above and showed no visible change in bacterial growth. The plates were incubated at 37 °C for 24 hours for bacteria and 48 hours for fungi. Compounds that exhibited significant growth inhibition zones (14 mm) using the double serial dilution technique were additionally examined for their minimum inhibitory concentrations (MICs).

Measurement of the minimum inhibition concentration (MIC)

The micro-dilution sensitivity tests in Müller-Hinton Broth (oxoid) and Sabouraud Liquid Medium (oxoid)

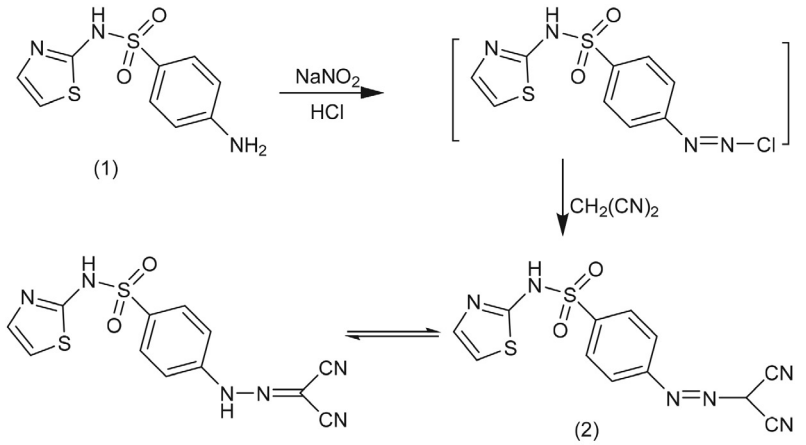
were used to determine antibacterial and antifungal activity. Stock solutions of the tested compounds, chloramphenicol, cephalothin and cycloheximide were prepared in DMSO at the concentration of 1000 mg/mL. Each stock solution was diluted with standard method broth to make serial twofold dilutions in the range 500–3.125 mg/mL. 10 mL of the broth containing about 106 CFU/mL of test bacteria were added to each well of the 96-well microtiter plate. The sealed microtiter plates were incubated for 24 hours at 37 °C for antibacterial activity and for 48 hours at 37 °C for antifungal activity in a humid chamber. At the end of the incubation period, the values of the minimum inhibitory concentrations (MIC) were recorded as the lowest concentrations of the substance that showed no visible turbidity. Control experiments with DMSO and uninoculated media were performed in parallel with the test compounds under the same conditions. The substance showed no visible turbidity.

3. Results and Discussion

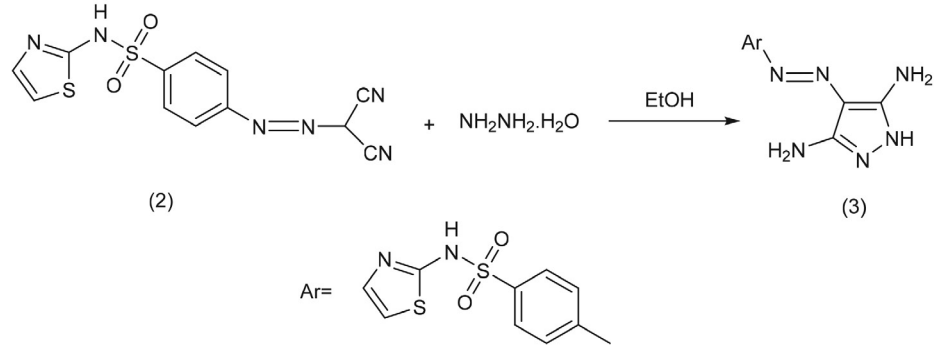
The synthetic strategies for obtaining the target compounds are shown in the Schemes 1–6. The main intermediate *N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyldicyanide (**2**) was prepared by diazotization of sulfathiazole, followed by coupling of the resulting diazonium salt with malononitrile.

The structure of compound **2** has been confirmed by its elemental and spectroscopic analysis. The IR spectrum of **2** showed absorption bands at 3234, 3188, 2225, 2216, 1654 and 1565 cm^{-1}, corresponding to two NH, two CN, C=N and N=N groups respectively. The mass spectrum of compound **2** showed a molecular ion peak at m/z 332 [M^+], which is consistent with the proposed structure. Recently, we have synthesized new heterocyclic compounds by studying the behavior of malononitrile derivatives towards different reagents.[18–22]

In continuation of this work we investigated the behavior of compound **2** towards hydrazine hydrate. The treatment of compound **2** with hydrazine hydrate in boiling ethanol yielded 4-((3,5-diamino-1*H*-pyrazol-4-yl)diazenyl)-*N*-(thiazol-2-ylbenzenesulfonamide (**3**). The structure of pyrazole derivative **3** was confirmed by its spectroscopic data and elemental analysis. The mass spectrum of compound 3 together with the elemental analysis confirmed the structure **3**. In addition, the IR spectrum of compound **3** showed the absence of an absorption peak for nitrile groups and the appearance of absorption bands at 3430, 3373, 3337, 3289 and 3219 cm^{-1} corresponding to two NH_2 and two NH groups, respectively, confirming the formation of pyrazole derivative **3** (Scheme 2).



Scheme 1. Synthetic pathway to sulfathiazole derivatives.

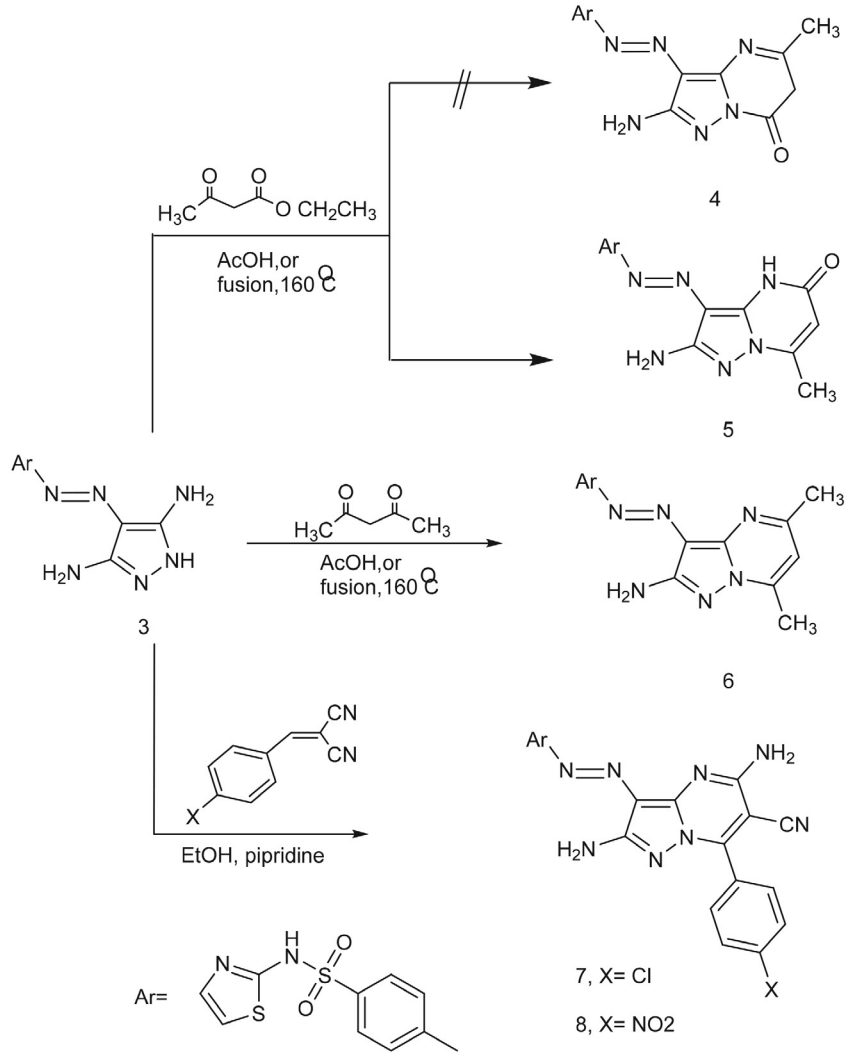


Scheme 2. Synthetic pathway to the aminopyrazole derivative **3**.

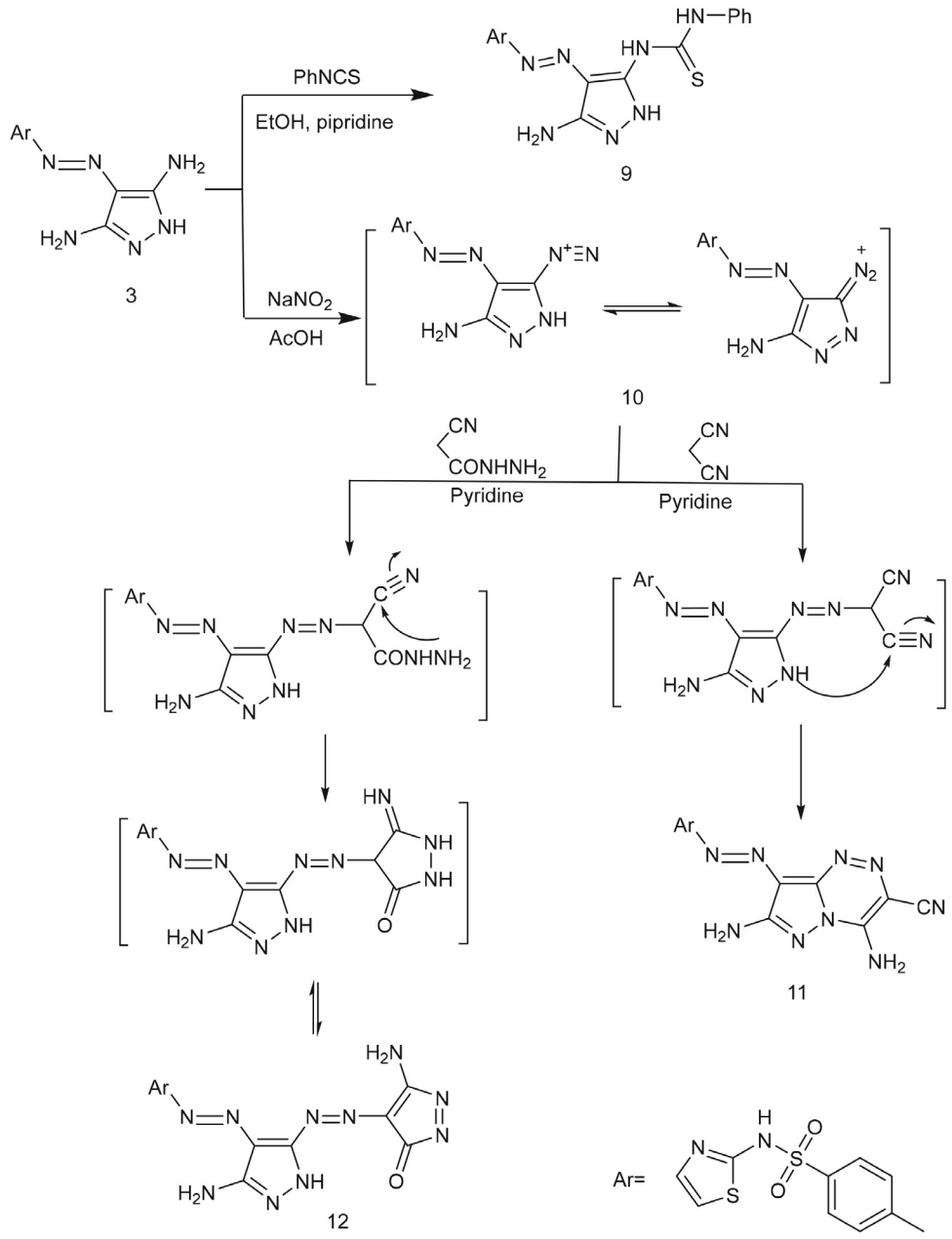
It has been found that pyrazolopyrimidines[23,24] and pyrazolotriazines[25] have major biological and medical activities as adenine analogs, antagonists and antitumor agents.[26–29] Therefore, we intend to prepare analogues of these compounds from 5-aminopyrazole derivatives (**3**) in high yield.

The treatment of 5-aminopyrazole derivative **3** with ethyl acetoacetate yielded a single product for which structures **4** or **5** seemed plausible (Scheme 3).[30,31] The ^{1}H NMR spectrum of the reaction product did not contain a singlet signal for CH_2 protons and instead two singlet signals were exposed at δ_H 7.26 and 11.46 ppm for the pyrimidine ring CH and NH protons, confirming structure **5** rather than structure **4**.[32] Structure **4** was also excluded on a chemical basis. Namely, that the reaction product did not condense with an aromatic aldehyde or couple with benzene diazonium salt, which happened promptly with active methylene azinones.[33]

In addition, compound **3** reacted with acetylacetone to form 4-((2-amino-5,7-dimethylpyrazolo[1,5-*a*]pyrimidin-3-yl)diazenyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**6**, Scheme 3). Compound **6** was confirmed by elemental analysis and spectroscopic analysis. The IR spectrum of **6** showed absorption bands at ν_{max} 3437, 3394, and 1560 cm^{-1} due to the NH_2 and N=N functions, respectively. In addition, its ^{1}H NMR spectrum showed four singlet signals at δ_H 2.08, 2.24, 5.74, and 7.08 ppm assigned to two methyl, NH_2, and CH pyrimidine protons, respectively. In addition, its mass spectrum showed the molecular ion peak at m/z 428 [M^+], corresponding to its correct molecular formula [$C_{17}H_{16}N_8O_2S_2$]. The reaction of the 5-aminopyrazole derivative **3** with arylidene malononitrile derivatives offered the pyrazolopyrimidines **7** and **8** (Scheme 3). Their structure was determined on the basis of their elemental and spectroscopic investigations. The mass spectra of compounds **7** and **8** showed molecular ion peaks that confirmed their expected structures. The IR spectra of both compounds showed stretching frequencies for NH_2, NH and CN groups, which confirmed their proposed structures.



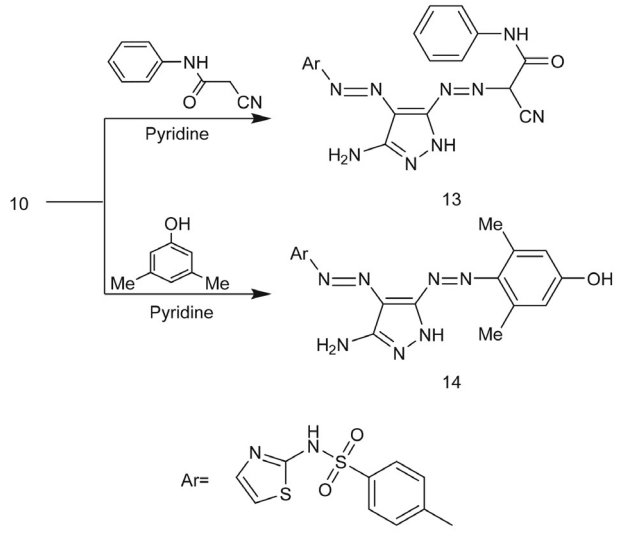
Scheme 3. Synthetic pathway to pyrazolo[1,5-*a*]pyrimidine derivatives.



Scheme 4. Synthetic pathway to pyrazolo[1,5-*c*]triazine and pyrazole derivatives.

The reaction of **3** with phenyl isothiocyanate yielded the pyrazolo-5-phenylthioureido derivative **9**, which was confirmed by analytical and spectroscopic data (Scheme 4). The coupling of diazonium salt **10** with malononitrile yields the pyrazolo[1,5-*c*]triazine **11**, while the coupling of **10** with 2-cyanoacetohydrazide yields pyrazolone derivatives **12**. The structures of **11** and **12** were confirmed based on their spectroscopic data. The IR spectrum of compound **11** showed stretching frequencies at 3447–3300 cm^{-1} due to NH_2 and NH groups and a sharp peak at 2227 cm^{-1} due to the CN group. Additionally, its mass spectrum showed a molecular ion peak at m/z 441, confirming the correct molecular formula. The IR spectrum of compound **12** showed bands at 3417–3311, 1678 and 1565 cm^{-1} corresponding to two NH_2, NH, CO and N=N groups, respectively. In addition, its mass spectrum showed a molecular ion peak at m/z 472, which is due to its molecular formula. Diazonium salt **10** was additionally reacted with 2-cyano-*N*-phenylacetamide and 3,5-dimethylphenol to obtain compounds **13** and **14**, respectively. The structure of compounds **13** and **14** was confirmed on the basis of elemental analysis and spectroscopic data, as already shown in the experimental part.

The significant biological and medical activity of the arylhydrazone of α-cyanoketone as an antituberculosis agent[34] and oxidative phosphorylation inhibitor[35] have



Scheme 5. Synthetic pathway to pyrazolo-4,5diazenyl derivatives.

stimulated research on this class of compounds. As part of our program, we report here on the synthesis of α cyanarylhydrazones **16** by treating hydrazine hydrate with *N*-methyl-*N*-(4-(*N*-(thiazol-2-yl)sulfamoyl)phenyl)carbonohydrazonoyldicyanide (**15**) (Scheme 6). The identity of compounds **15** and **16** was confirmed by their spectroscopic analysis.

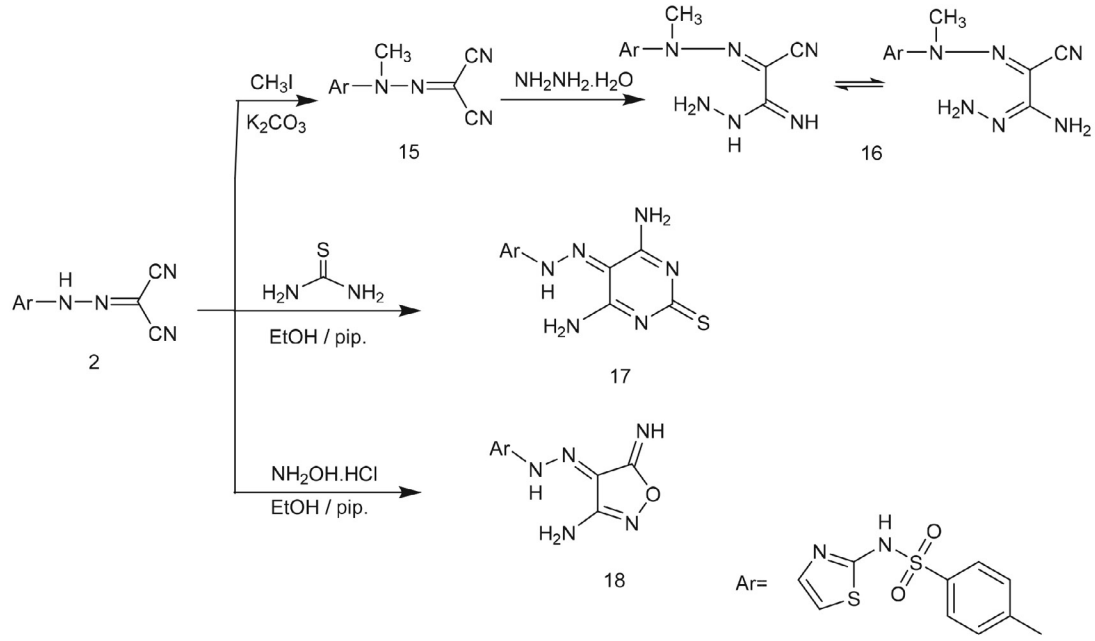
On the other hand, the reaction of compound **2** with different nucleophiles, for example thiourea and hydroxylamine hydrochloride, enabled 4-(2-(4,6-diamino-2-thioxopyrimidin-5(2*H*)-ylidene)hydrazinyl)-*N*-(thiazol-2-yl) benzenesulfonamide (**17**) and 4-(2-(2-(3-amino-5-iminoisoxazol-4(5*H*)-ylidene)hydrazinyl)-*N*-(thiazol-2-yl)benzenesulfonamide (**18**), respectively. The IR spectrum of **17** showed the presence of two NH_2 and two NH absorption bands at 3434–3400 cm^{-1}, the C=S group at 1325 cm^{-1} and the absence of CN groups. The mass spectra of compounds **17** and **18** showed a molecular ion peak that confirmed proposed structures.

4. Antimicrobial Evaluation

The synthesized compounds were evaluated against *Bacillus subtilis* and *Staphylococcus Aureus* as Gram-positive bacteria and against *Escherichia coli* and *Pseudomonas Aeruginosa* as Gram-negative bacteria. They were also tested for their in vitro antifungal potential against strains of *Fusarium oxysporum* and *Candida albicans*. The agar diffusion method with chloramphenicol, cephalothin and cycloheximide as reference drugs was used to determine the antibacterial and antifungal activity.

The results were recorded for each compound tested as the normal diameter of the bacterial or fungal growth inhibition zones (IZ) around the disks in mm. The MIC measurement was determined for compounds that had significant growth inhibition zones (>14 mm) using a twofold serial dilution method.[36,37] The values for MIC and inhibition zone diameters are shown in Table 1. Most of the compounds tested showed variable inhibitory activity for the growth of the Gram-positive and Gram-negative strains of bacteria tested and against the antifungal strain. In general, most of the compounds tested showed better activity against the Gram-positive than against the Gram-negative strains.

Regarding the structure-activity relationship of sulfathiazole derivatives against Gram-positive bacteria, the re-



Scheme 6. Synthetic pathway to pyrimidine and isoxazole derivatives.

Table 1. Minimum inhibiton concentration (MIC, μg/mL) and inhibition zone (mm) of the synthesized compounds.

Compound No.	MIC in μg/mL, and inhibition zone (mm)				
	Bacteria				Fungi
	Gram-positive bacteria		Gram-negative bacteria		
	B. subtilis	*S. aureus*	*E. coli*	*P. aeruginosa*	*C. albicans*
2	3.125 (40)	6.25 (37)	100 (15)	50 (19)	3.125 (36)
3	25 (27)	50 (15)	100 (15)	100 (16)	6.25 (28)
5	3.125 (45)	6.25 (38)	25 (25)	12.5 (33)	3.125 (40)
6	12.5 (33)	50 (14)	50 (20)	50 (19)	50 (20)
7	12.5 (32)	50 (20)	100 (15)	100 (15)	100 (16)
8	3.125 (44)	6.25 (37)	100 (14)	50 (20)	25 (19)
9	12.5 (32)	50 (20)	100 (15)	100 (15)	6.25 (30)
11	3.125 (41)	6.25 (37)	100 (15)	100 (16)	6.25 (25)
12	6.25 (38)	6.25 (30)	100 (14)	100 (15)	6.25 (26)
13	12.5 (32)	6.25 (38)	100 (15)	50 (19)	6.25 (30)
14	6.25 (37)	6.25 (37)	100 (15)	100 (15)	12.5 (32)
15	6.25 (38)	6.25 (37)	100 (15)	50 (19)	50 (20)
16	6.25 (38)	6.25 (37)	100 (15)	50 (19)	100 (16)
17	3.125 (40)	6.25 (37)	100 (15)	50 (19)	50 (20)
18	3.125 (41)	6.25 (38)	100 (15)	50 (19)	100 (16)
Chloramphenicol	3.125 (44)	3.125 (44)	6.25 (37)	6.25 (38)	NT
Cephalothin	6.25 (36)	6.25 (37)	6.25 (38)	6.25 (37)	NT
Cycloheximide	NT	NT	NT	NT	3.125 (42)

MIC values with SEM = 0.02 (the lowest concentration that inhibited bacterial growth). NT: Not tested.

sults showed that compounds **2**, **5**, **8**, **11**, **17** and **18** showed a broad antibacterial profile against the organisms tested and were equivalent to chloramphenicol in inhibiting the growth of *B. subtilis* (MIC, 3.125 μg/mL), while the activity was 50% lower than chloramphenicol against *S. aureus*. On the other hand, compounds **3**, **6**, **7**, **9**, **12**, **13**, **14**, **15** and **16** showed moderate growth-inhibiting activity against Gram-positive bacteria, as shown by their MIC values (6.25–50 μg/mL). Of these compounds, **12**, **14**, **15** and **16** showed good growth-inhibiting activity against *B. subtilis* (MIC, 6.25 μg/mL), while compounds **6**, **7**, **9** and **13** showed relatively good growth-inhibiting profiles against *B. subtilis* (MIC, 12.5 μg/mL), accounting for about 25% of the activity of chloramphenicol and 50% of cephalothin against the similar organism. The antibacterial activity of compound **6** showed a weak growth-inhibiting effect against the tested Gram-negative bacteria (MIC, 50nμg/mL). As for the activity of sulfathiazole derivative **2** against antifungal strains, the results showed their moderate to good antifungal activity.

Of the compounds studied, compounds **2** and **5** were equivalent to cycloheximide in inhibiting the growth of *C. albicans* (MIC 3.125 μg/mL). In contrast, compounds **3**, **9**, **11**, **12** and **13** showed 50% lower activity than cycloheximide in inhibiting the growth of *C. albicans* (MIC 6.25 μg/mL), while the activity of compound **14** was 25% lower than that of cycloheximide against *C. albicans* (MIC 12.5 μg/mL). In general, the tested compounds were more active against Gram-positive bacteria than Gram-negative bacteria, and it could be argued that the antimicrobial activity of the compounds is related to the cell wall structure of the bacteria. Indeed, the cell wall is essential for the survival of bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan. Gram-positive bacteria have a thick cell wall that contains many layers of peptidoglycan and teichoic acids, but in contrast, Gram-negative bacteria have a relatively thin cell wall that consists of a few layers of peptidoglycan and is surrounded by a second lipid membrane that contains lipopolysaccharides and lipoproteins. These differences in cell wall structure can lead to differences in antibacterial susceptibility, and some antibiotics can only kill Gram-positive bacteria and are inactive against Gram-negative pathogens.[38]

By comparing the antimicrobial activity of the compounds reported in this study with their structures, the following structure-activity relationships (SAR) were postulated:

– The presence of a basic sulfathiazole skeleton is necessary for the broad spectrum of antimicrobial activity.

– The introduction of electron-withdrawing groups, such as CN or NO_2, increases the antimicrobial activity.

– Compounds **2**, **8**, **11**, **17** and **18** showed the highest antimicrobial activity, while the other compounds showed weak to moderate antimicrobial activity.

5. Conclusion

The present study reports on the efficacy of pyrazolo[1,5-*a*]pyrimidine and pyrazolo[1,5-*c*]triazine derivatives containing a sulfathiazole unit. The simple synthesis strategy and the very good yields of the compounds produced are the main advantages of the protocol presented.

The newly synthesized compounds showed moderate to good antibacterial and antifungal activities.

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Povzetek

Avtorji poročajo o pripravi večjega števila derivatov pirazolo[1,5-*a*]pirimidina z reakcijo 4-((3,5-diamino-1*H*-pirazol-4-il)-diazenil)-*N*-(tiazol-2-il))-benzensulfonamida z nekaterimi bifunkcionalnimi nukleofili, kot so etil acetoacetat, acetilaceton ali derivati arilidenmalononononitrila. Strukture novo sintetiziranih spojin so določili na podlagi njihovih IR, ^{1}H in ^{13}C NMR ter masnih spektroskopskih podatkov. Večina pripravljenih spojin je pokazala dobro protibakterijsko in protiglivično delovanje.